positions on the polymeric carrier and wherein the carrier is non-immunologically reactive when the monomeric units are amino acids.

REMARKS

In view of the preceding amendments and the comments which follow, and pursuant to 37 CFR §1.111, amendment and reconsideration of the Official Action of August 15, 2000 is respectfully requested by Applicants.

Amendments to claims

Claims 90-99 have been cancelled without prejudice.

Claims 72, 83-85 and 87 have been amended. Support for the "non-immunologically reactive" recitation added to claim 72 can be found in the specification at page 16, lines 2-7; no new matter has been added.

New claims 100-102 have been added. Claims 100 and 101 are drawn to a conjugate comprising a synthetically-made polymeric carrier having monomeric units selected from the group consisting of nucleotides, nucleotide analogues and amino acids, the conjugate containing hapten molecules and marker groups or solid phase binding groups, wherein the hapten molecules and the marker groups or solid phase binding groups are coupled to reactive side groups at predetermined positions on the polymeric carrier. In claim 100, the conjugate is characterized by comprising more than one hapten molecule, and in claim 101, the conjugate is characterized by reciting that the side groups coupling the hapten molecules and the marker groups or solid phase binding groups are alike. Support for the recitation in claim 100 of more than one hapten molecule is found in the specification on page 16, last 3 lines. Support for the recitation in claim 101 describing that the side groups coupling the hapten molecules and the marker groups or solid phase binding groups are alike can be found in Example 3. Conjugates I and II described therein contain estradiol as hapten and ruthenium conjugate as marker groups,

each coupled to the ε-amino group of the lysine side chain. New claim 102 recites the nucleotide analogue limitation now deleted from claim 72 by the present amendment.

Rejections under 35 USC §112, first paragraph

The examiner has rejected claims 72-77, 80-81 and 83-88 under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The examiner states that claims 72-77, 80-81 and 83-88 recite that the monomeric units of the carrier are selected from at least one of nucleotides, nucleotide analogs and amino acids and that this would result in carriers having a mixture of different monomers in the same carrier. The disclosure as originally filed does not appear to support carriers having such a mixture.

In reply, Applicants first respectfully refer the examiner to the specification at page 7, lines 23-27, where carriers having a mixture of different monomers in the same carrier are described, i.e., double-stranded carriers with at least one peptidic nucleic acid strand and a nucleic acid strand, e.g., a DNA strand. For the purpose of complete clarity, however, Applicants have amended claim 72, and claims 73-77, 80-81 and 83-88 depending ultimately from claim 72, by reciting the Markush grouping in correct form. The examiner's reconsideration of his rejection is respectfully requested.

The examiner states that claims 72, 86 and 87 have been rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The examiner states that Applicants' claims recite conjugates where in the haptens are hormone metabolites; however, the specification discloses only a few subgeneric examples of hormone metabolites on page 8.

Applicants have amended claim 87 by removing the term "hormone metabolites". With respect to claim 72 and 86, Applicants respectfully seek the examiner's clarification of his rejection, as claims 72 and 86 do not recite species of hapten molecules. The examiner's reconsideration of his rejection of claims 72, 86 and 87 is respectfully requested by Applicants.

Rejections under 35 USC §112, second paragraph

The examiner has rejected claims 72-77, 80-81 and 83-88 under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

The examiner states that claims 72-77, 80-81 and 83-88 are vague and indefinite in their recitation that the hapten and the marker groups or solid phase binding groups are different from each other. Applicants have removed the vague recitation and thereby overcome the examiner's rejection. The examiner's reconsideration of his rejection is respectfully requested.

Claims 83 and 84 have been rejected by the examiner in their recitation that the polymeric carriers contain at least one of a positive charge carrier and a negative charge carrier. Applicants have amended claim 83 and 84 by reciting the Markush grouping in correct form and by more clearly reciting the structure. Applicants respectfully request the examiner's reconsideration of his rejection.

Claim 85 has been rejected by the examiner for the reason that its recitation of an essentially helical structure is vague and indefinite. Applicants respectfully draw the examiner's attention to the specification at page 11, lines 21-28, describing the advantageous nature of a helical structure of the carrier backbone. For further clarity, Applicants have amended claim 85 so that it now recites a helical structure rather than an essentially helical structure. The Examiner's reconsideration of his rejection is respectfully requested by Applicants.

Claim 87 has been rejected for its recitation of a hormone metabolite. Since this terminology has been deleted by the present amendment, the rejection is now avoided and the examiner's reconsideration is requested.

Rejection under 35 USC §102

The examiner has rejected claims 72, 74-77, 80-81, 83 and 86 under 35 USC §102(b) as being anticipated by Bredehorst *et al.* (*Analytical Biochemistry 193*:2, 272-279, 1991, hereinafter "Bredehorst"). The examiner states that Bredehorst teaches insulin (a polymeric carrier comprising amino acids) conjugated to a dinitrophenol (DNP) group and three fluorescein molecules coupled to reactive side groups (carboxyl or amine) at predetermined positions, and that therefore, Bredehorst anticipates the invention of claims 72, 74-77 and 80-81. The examiner further states that, as the carrier has negatively charged sulfate groups, it anticipates claim 83, and as the molecular weight of DNP is in the range of 100-2000 daltons, claim 86 is anticipated. The examiner also notes that the recitation "wherein the polymeric carrier is prepared by synthesis on a solid phase" does not limit the product.

Via the present amendment, Applicants recite the limitation in claim 72, and in claims 74-77, 80-81, 83 and 86 depending ultimately therefrom, wherein "the carrier is non-immunologically reactive when the monomeric units are amino acids". Support for the amendment is found in the specification on page 16 at lines 2-7. This limitation distinguishes the invention over the disclosure of Bredehorst, which teaches a backbone sequence that is a naturally occurring peptide, i.e., the insulin A-chain. This insulin A-chain would very much interfere with an immunological test on patients having anti-insulin antibodies, which is quite possible with diabetic patients. Bredehorst does not teach the synthetic, non-immunologically reactive amino acid sequences of the present invention, nor does Bredehorst teach the nucleotide and nucleotide analogue sequences of the present invention.

Applicants submit that the examiner's rejection has now been overcome, and they respectfully request the examiner's reconsideration.

Rejection under 35 USC §103

The examiner has rejected claims 72-77, 80-81, 83-84 and 86 under 35 USC §103(a) as being unpatentable over Bredehorst in view of US Patent No. 5,310,687 to Bard *et al.*, (hereinafter "Bard"). Bredehorst teaches a naturally-occurring polymeric carrier (insulin A-chain) comprised of amino acids to which is attached a hapten, a fluorophore and a hydrophilic group. Bard teaches the use of a luminescent metal chelate as a marker in immunoassays.

Applicants argue that there is no suggestion or motivation leading a person skilled in the art to which the present invention belongs to combine a luminescent metal chelate with the amino acid carrier molecule of Bredehorst. Further, even if one were to combine the two references, the present invention is still not achieved. Neither Bredehorst nor Bard teaches a non-immunologically reactive amino acid backbone carrier of the present invention. Further, neither Bredehorst nor Bard teaches the nucleotide or nucleotide analogue carrier of the present invention. Applicants argue that the examiner's *prima facie* case of obviousness has not been made, and they respectfully request the examiner's reconsideration of his rejection.

The examiner has rejected claims 72, 74-77, 80-81, 83 and 85-88 under 35 USC §103(a) as being unpatentable over PCT application WO 92/20703 to Buchardt *et al.* (hereinafter "Buchardt") in view of Bredehorst. Buchardt teaches a peptide nucleic acid (PNA) comprising a peptide backbone bearing a plurality of nucleobases attached via a linker to the backbone. Buchardt teaches that PNA molecules may be conjugated to reporter ligands or recognition ligands; however, as the examiner notes, Buchardt does not explicitly recite incorporating both marker groups and haptens or solid phase binding groups into a single polymeric conjugate molecule.

Bredehorst teaches an insulin A-chain backbone with a hapten and a marker group both incorporated along the backbone. There is no teaching in either Bredehorst or Buchardt, however, of how one would incorporate both haptens and marker groups on the backbone of Buchardt, or how one would incorporate the hapten and marker groups of Bredehorst on the PNA backbone taught by Buchardt. Bredehorst does not teach the use of protecting groups having different functions in the same molecule, as insulin A-chain has a defined sequence of 21 amino acids with one amino functionality and three carboxyl functionalities exactly 4, 17 and 21 amino acids away from the terminal amino, the site used for hapten coupling. Only the teachings of the present invention describe how to construct an amino acid backbone with predetermined sites for attachment of haptens and marker groups, and only the teachings of the present invention describe the incorporation of multiple hapten groups along the same backbone. The examiner's *prima facie* case of obviousness has not been made, and Applicants respectfully request the examiner's reconsideration of his rejection.

The examiner has rejected claims 72-77, 80-81 and 83-88 under 35 USC §103(a) as being unpatentable over Buchardt in view of Bredehorst and further in view of Bard.

As argued above, Buchardt in view of Bredehorst fails to teach or suggest the present invention, and Bard does not provide the necessary teaching or motivation missing from Buchardt and Bredehorst. A person skilled in the art would not combine Bredehorst with Buchardt since Bredehorst only describes the derivatization of a naturally occurring peptide (insulin A-chain). Therefore, a person skilled in the art has no reason to combine this disclosure with Buchardt describing the modification of peptide nucleic acid carriers. The examiner's *prima facie* case of obviousness has not been made, and Applicants respectfully request the examiner's reconsideration of his rejection.

* * * * * *

Applicants submit that their application is now in condition for allowance, and favorable reconsideration of their application in light of the above amendments and remarks is respectfully requested. Allowance of claims 72-77, 80-81, 83-88, and 100-102 at an early date is earnestly solicited.

The examiner is hereby authorized to charge any fees associated with this Amendment to Deposit Account No. 50-0877. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Date: Feb 15, 2001

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